Review

COVID-19: Transmission, prevention, and potential therapeutic opportunities

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ABSTRACT

The novel coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global challenge. Despite intense research efforts worldwide, an effective vaccine and viable treatment options have eluded investigators. Therefore, infection prevention, early viral detection and identification of successful treatment protocols provide the best approach in controlling disease spread. In this review, current therapeutic options, preventive methods and transmission routes of COVID-19 are discussed.

1. Introduction

Although the emergence of new coronavirus diseases, probably originating from bats in China, had been predicted by early March 2019 [1], no international preventive action was taken. Finally, after several cases of pneumonia with an unfamiliar etiology were observed at the end of 2019, the National Health Commission of China released more details about the epidemic in early 2020 [2]. The causative virus was initially called "novel coronavirus 2019" (2019-nCoV) by the World Health Organization (WHO), but it was then renamed as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG), and the disease called "coronavirus disease 2019" (COVID-19) by WHO [3]. It is thought that the Hunan seafood market in Wuhan city in China was the origin of the outbreak. Although it had been proposed that the COVID-19 patients in China might have utilized infected animals as a foodstuff, or might have visited the seafood market, further investigation revealed that some patients had not visited the seafood market. Therefore, the human-to-human transmission of this virus through coughing, sneezing, and the spread of respiratory droplets or aerosols was accepted. In addition, almost all countries in continents throughout the world reported disease spread caused by aerosol penetration into the upper the respiratory tract and lungs via inhalation [4,5]. There followed a rapid growth in the number of cases all around the world. A mathematical model examined whether the control of SARS-CoV-2 infection could be achieved by isolating affected patients, and tracking their contacts with other individuals. This model concluded that isolating people and reviewing their contacts would be insufficient to control the COVID-19 pandemic within three months, because there would be too much delay between the onset of symptoms and isolation [6]. Thus, observing preventive measures, especially isolation and lockdown, would be essential.

SARS-CoV-2 is highly contagious, and there has not yet been any vaccine or effective treatment that has received approval. So, the best solution for controlling the pandemic will be the simultaneous application of preventive methods, sensitive diagnostic approaches, and using current available drugs, while still developing novel treatments [7–9]. This study presents the latest information about COVID-19 transmission, prevention, and potential therapeutic options.

2. SARS-CoV-2 characteristics

SARS-CoV-2 is an enveloped, positive-sense, and single-stranded 29.9 kb RNA beta-coronavirus [10,11]. Investigation of the SARS-CoV-2 genome proved that it has 88% similarity with the bat-SL-CoVZC45 and bat-SL-CoVZXC21 sequences, and was 96.2% identical to another bat

CoV RaTG13 [12]. However, some recent investigations have suggested that pangolins that were smuggled from Malaysia to China, along with other possible intermediate hosts like turtles or snakes could be the direct origin of the virus instead of a bat [13].

Moreover, the protein-coding genes of SARS-CoV-2 have 79.5% and 51% sequence similarity to SARS-CoV and MERS-CoV, respectively. The SARS-CoV-2 virus employs the Angiotensin-Converting Enzyme 2 (ACE2) receptor for cellular entry, similar to SARS-CoV [3,14]. Therefore, previous treatments that were used to control the SARS-CoV and MERS-CoV epidemics, might also be effective in SARS-CoV-2.

3. Clinical consequences

The first symptoms are commonly recognized as fever, dry cough, tachypnea, and shortness of breath [15]. Although diarrhea was present in about 20–25% of patients with MERS-CoV or SARS-CoV infection, intestinal symptoms are rarely seen in patients with COVID-19. In another study, confusion, chest pain, vomiting, and nausea were also reported as COVID-19 symptoms [16]. Other symptoms include, sore throat, sneezing, nasal congestion, sputum production, anosmia and dyspepsia, rash on the skin, or discoloration of fingers or toes, and viral conjunctivitis. Some laboratory studies have shown the occurrence of cytokine storm, sepsis, and RNAaemia in COVID-19 [17,18].

Clinical chemistry studies have shown increases in lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine transaminase (ALT), C-reactive protein (CRP), creatine kinase (CK), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, D-dimer level, procalcitonin, urea, and creatinine. Decreases in hemoglobin, lymphocyte count, eosinophil count, and serum albumin have been detected in COVID-19 patients [17].

The most common radiological findings in patients with COVID-19 were a ground-glass opacity in the lungs [19]. Moreover, SARS-CoV-2 can affect the cardiovascular system [16], gastrointestinal tract [20], and can cause acute kidney failure [2,19]. Moreover, evaluation of liver manifestations in 148 patients with COVID-19 indicated that more than one-third of the COVID-19 patients admitted to the hospital had abnormal liver function, and these patients were hospitalized for a more extended period [21]. It must be mentioned that it is likely that a substantial number of asymptomatic patients can be carriers of the virus. The variable clinical manifestations and outcomes underline the importance of adhering to hygienic and preventive principles, in addition to finding and developing new sensitive diagnostic approaches and therapeutic options.

4. Infection in children

Unlike adults, children with COVID-19 have milder symptoms and better clinical outcomes [22]; among the COVID-19 patients under 18 years of age, children under one year old seem to be at the highest risk of the severe form of the disease [23]. Although early studies showed that children with COVID-19 were less likely to develop severe symptoms than other age groups, one new study has shown that children are as likely to develop COVID-19 as adults [24]. So, prevention and finding appropriate treatment for children is as important as for adults.

In one study, 1391 children with a median age of 6.7 years were surveyed, and 171 were diagnosed with COVID-19. Intensive Care Unit (ICU) and mechanical ventilation were needed for only three children, who had underlying conditions. By March 8th, 2020, one child with intussusception had died, 21 children remained in a stable condition in the ward, and 149 cases were discharged [25].

It should be mentioned that recently scientists and clinicians have reported that young infants who were diagnosed with COVID-19, also had classic Kawasaki disease (KD) or a KD-like disease, which indicates that more investigation into the clinical manifestations of pediatric COVID-19 and its potential association with KD is needed [26].

5. Transmission of COVID-19

SARS-CoV-2 can spread through both direct means (droplet and human-to-human transmission) and by indirect contact (contaminated objects and airborne contagion). Meanwhile personal protective equipment (PPE) could also be the source of airborne infections [27]. As mentioned before, person-to-person spread of SARS-CoV-2 is supposed to occur mainly via respiratory droplets, when a patient coughs, sneezes, or even talks or sings. Droplets typically cannot traverse more than six feet (almost two meters) and remain in the air for a limited time. However, SARS-CoV-2 remains intact and contagious in droplets (less than five microns in diameter) and can be suspended in the air for up to three hours [28]. Therefore, airborne isolation, room ventilation, and appropriate application of disinfectant (especially in toilets) might restrict aerosol spread of the virus [29].

COVID-19 can occur if a person touches a surface contaminated with SARS-CoV-2, and then the hands come into direct contact with mucous membranes such as the eyes, nose, or mouth [30]. Thus, sufficient washing of hands with soap and water or hand sanitizers is recommended.

The reported contagion rates from a patient with symptomatic infection vary by location and efficiency of infection control measures. Based on a joint WHO-China report, the rate of secondary COVID-19 infection ranged from one to five percent among tens of thousands of confirmed patients in China [30].

The spread of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period), without any radiological findings, has also been reported [31–33]. Therefore, there is a need for improvements in rapid and sensitive diagnostic methods for detecting infected individuals.

In a study on four hospital staff who became infected, although each patient had at least two negative tests, the RT-PCR was still positive from 5 to 13 days after being discharged [34]. Also, viral shedding in the stool likely occurs up for to five weeks (the longest time of shedding was 37 days [35] and in deceased patients until the moment of death) with a mean of 11.2 days after the respiratory tract test was negative [36]. So, because SARS-CoV-2 can be transmitted from recovered patients, it is wise to change the current discharge criteria. The current discharge criteria are as follows:

(1) Two consecutive RT-PCR negative results in at least a 24 h interval; (2) Complete resolution of the patient's acute exudative pulmonary lesions on chest Computed Tomography (CT) examination; (3) Normalization of temperature for over 72 h; and (4) Resolution of the patient's respiratory symptoms [34,37].

Although SARS-CoV-2 RNA has been discovered in blood and stool samples [38] and living SARS-CoV-2 has been cultured from stool in some COVID-19 patients [39], a joint WHO-China report indicated that fecal-oral transmission route did not appear to be an important factor in the spread of infection [30].

It should be mentioned that a study of semen and testicular specimens of COVID-19 patients suggested that SARS-CoV-2 could not be transmitted through sexual contact [40].

As pregnant women are at a high risk of contracting COVID-19, investigating the possible vertical transmission of COVID-19 is important. An infant delivered from an affected mother was reported to test negative for seven duplicate samples of neonatal blood, stool, and oropharynx [41]; however, recent studies showed immunoglobulin M (IgM) antibodies to SARS-CoV-2 were present in newborn infant blood; so, possible transmission of SARS-CoV-2 from mother to fetus could not be ruled out [42,43].

Although it is unknown whether the SARS-CoV-2 was transmitted from infected animals (civet cat, snake, or other species) to humans at the Huanan seafood market or not, there is a clear possibility for animal-to-human transmission [44]. Ferrets, cats, dogs, and other domesticated animals are susceptible to SARS-CoV-2 [45]. It has been demonstrated that cats can be infected with SARS-CoV-2 and transmit it

to other cats. Nevertheless, it is not yet clear if cats can transmit the virus to their owners; so at present this not a problem for cat owners. Moreover, ducks, pigs, chickens, and dogs are not likely to be infected. However, it should be mentioned that a German shepherd pet dog died (the cause of death could not be determined as the owner declined to conduct an autopsy) two days after the owner was in COVID-19 quarantine [46]. So, possible animal-to-human transmission of the virus must be taken into account.

Based on the above-mentioned evidence, transmission of the virus could be more complicated than that seen in previous pandemics. The virus is highly contagious, and there is no successful treatment or a vaccine. Also, a relatively long incubation period, presence of asymptomatic patients, and continued viral shedding after recovery all underline the importance of home quarantine through lockdown of the entire society like the Chinese government carried out [47].

6. Temperature and humidity and SARS-CoV-2 infection

One study investigated the relationship between the mean daily average temperature and the average rate of increase of new patients with COVID-19. Five countries (Iran, Italy, Germany, Spain, and United States) were studied. To minimize the impact of confounding factors like the imposition of government measures or cultural differences between these countries, different areas in each country were compared separately. The results of this study found that in all studied areas, a significant difference in the average daily air temperature between the two regions was associated with a substantial difference in the daily average cumulative rate of new patients in those two regions [48].

In addition, the average temperature and humidity of infected cities were found to be 5 °C to 11 °C and 47 to 79%, respectively, and the optimum temperature and humidity for the survival of SARS-CoV-2 *in vitro* were 4 °C and 20 to 80%, respectively. Also, the average temperature in the contaminated cities was never below zero degrees Celsius. Additionally, the virus spread in the latitude corridor was 30 to 50°north (South Korea, Japan, Iran, and North Italy). Furthermore, at this time, the SARS-CoV-2 had not been able to spread quickly in southern China [49].

Although the above-mentioned reports suggest a relationship between temperature and the distribution of the virus, comparing the global climate and COVID-19 distribution maps [50,51], it could be concluded that there was no significant relationship between temperature, humidity, and the virus distribution.

7. Preventive approaches

The WHO has stated that education, isolation, prevention, controlling the transmission, and treatment of infected persons are the critical steps in controlling contagious diseases like COVID-19 [52]. It is possible to minimize the spread of infection by making the following recommendations.

Staying at home (home quarantine) and avoiding any direct contact with any healthy (possible asymptomatic patients) or infected person, which has been called shielding; avoiding nonessential travel; observing social distancing rules like avoiding crowded public places and maintaining at least two meters of distance between each person, especially if they are coughing or sneezing; avoiding shaking hands when greeting others; frequently washing hands for at least 20 s with soap and water or hand sanitizer with at least 60% alcohol, especially after touching common surface areas, using the bathroom, or shaking hands, avoiding touching eyes, nose, and mouth with unwashed hands; and disinfecting surfaces using household sprays or wipes.

It should be mentioned that due to the long incubation period and presence of asymptomatic patients, using a medical mask (especially N95) or a respirator (especially FFP3) could be recommended. Also, sterilizing the used respirator, only reusing it for a limited time, and proper disposal of the used masks, have been recommended. Although

respirators (the protective classes, including FFP1, FFP2, and FFP3 [53]) are produced as single-use items, they could be used again for a limited time unless there is a risk for contamination through the deposition of infectious particles on the surface [54]. When the respirator becomes soiled or wet with bodily fluids or it can no longer be appropriately fitted, or if breathing via the respirator becomes difficult, it should be discarded. Also, masks should be discarded after being used during an aerosol-generating procedure (AGP). Until now, manufacturers have had no reason to disinfect masks or to produce masks for repeated use. However, there is a vital need to be able to disinfect masks and reuse them. SARS-CoV-2 remains viable in the environment, including on the surface of different materials like cardboard, iron, or tissue for some time. This suggests that there is a risk for rapid contamination of the outer surface of respirators and surgical masks. Contamination of the respirator surface could be prevented through placing a medical mask over it, or wearing a face shield that can be cleaned. Because of the severe contamination of respirators and surgical masks in the COVID-19 pandemic, several methods could be considered for the sterilization of used masks, including steam, hydrogen peroxide, or radiation.

Besides, the use of medical shields or wearing protective suits is recommended, especially for health care workers. It should be mentioned that wearing gloves in public is not an adequate protection against COVID-19, because gloves can easily be contaminated. So, frequent washing of hands is the best way to protect against SARS-CoV-2 infection [55].

A study in six departments of a hospital in Wuhan, China demonstrated that the use of N95 masks, disinfectants, and handwashing by doctors and nurses were effective in preventing against COVID-19 infection [56].

In terms of vaccines, there are a large number of vaccination strategies against SARS-CoV, MERS-CoV being tested in animals, including a live-attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and proteins vaccines (1 1 6). Although, until now, there has not been any approved vaccine against SARS-CoV-2, several clinical trials have been launched for testing the effects of various vaccines against SARS-CoV-2.

8. COVID-19 therapeutic options

Huang *et al.* [57] reported that acute respiratory distress syndrome (ARDS) was the most common complication in COVID-19 patients [58], followed by anemia, acute cardiac injury, and secondary infections. Hence, empirical antibiotics, antiviral drugs, and systemic corticosteroids are used as treatments [59]. Moreover, Holshue *et al.* [60] suggested the use of invasive mechanical ventilation for patients with intractable hypoxemia. So, the treatments of patients with COVID-19 infection are mainly symptomatic in nature.

It should be mentioned that the panel of National Institutes of Health (NIH) does not recommend the application of any agent for pre- or post-exposure prophylaxis against SARS-CoV-2 outside the setting of a clinical trial [61]. Except for the clinical trials, some medications are not recommended for use in the clinic, like the combination of Hydroxychloroquine and Azithromycin because of the potential for toxicity. Other conceivable treatments are not recommended such as Lopinavir/Ritonavir or other protease inhibitors (used for human immunodeficiency virus (HIV)) because of unfavorable pharmacodynamics and negative clinical trial data, Interferons because of lack of efficacy in the treatment of SARS and MERS, Janus kinase inhibitors (e.g., Baricitinib [62]) because of their broad immunosuppressive effects, and systemic corticosteroids during the treatment of mechanically ventilated patients with COVID-19 without ARDS.

Scientists are trying hard to develop new potential therapeutic strategies, consisting of monoclonal antibodies, vaccines, peptides, Interferon-based therapies, protease inhibitors, and small-molecule drugs to defeat the COVID-19 pandemic. However, it might take several

Table 1

Clinical trials for evaluating preventive and therapeutic options against SARS-CoV-2 (up to March 29th 2020).

Clinical trials	Identifier	Status	country
Tocilizumab in COVID-19 Pneumonia	NCT04317092	Recruiting	Italy
Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	NCT04315298	Recruiting	United States
A Pilot Study of Sildenafil in COVID-19	NCT04304313	Recruiting	China
ACE Inhibitors, Angiotensin II Type-I Receptor Blockers, and Severity of COVID-19 (CODIV-ACE)	NCT04318418	Not recruiting	Italy
Treatment of COVID-19 Cases and Chemoprophylaxis of Contacts as Prevention (HCQ4COV19)	NCT04304053	Recruiting	Spain
The Use PUL-042 Inhalation Solution to Prevent COVID-19 in Adults Exposed to SARS-CoV-2	NCT04313023	Not yet recruiting	
The Use of Angiotensin-Converting Enzyme Inhibitors and Incident Respiratory Infections, Are They Harmful or Protective?	NCT04322786	Not yet recruiting	
Nitric Oxide Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19.	NCT04290871	Withdrawn	
Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID-19	NCT04322396	Not yet recruiting	
Identifying Critically-ill Patients With COVID-19 Who Will Benefit Most From Nutrition Support Therapy: Validation of the NUTRIC Nutritional Risk Assessment Tool	NCT04274322	Not yet recruiting	
Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial - CORIMUNO-19 - SARI	NCT04324073	Not yet recruiting	France
Hydroxychloroquine Versus Placebo in Patients Presenting COVID-19 Infection and at Risk of Secondary Complication: a Prospective, Multicentre, Randomised, Double-blind Study	NCT04325893	Not yet recruiting	
Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients	NCT04293887	Not yet recruiting	
Xiyanping Injection for the Treatment of New Coronavirus Infected Pneumonia	NCT04275388	Not yet recruiting	
Chloroquine Diphosphate for the Treatment of Severe Acute Respiratory Syndrome Secondary to SARS-CoV2	NCT04323527	Recruiting	Brazil
Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection	NCT04283461	Recruiting	United States
Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	NCT04322682	Recruiting	Canada
Tocilizumab for SARS-CoV2 Severe Pneumonitis	NCT04315480	Not recruiting	Italy
Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	NCT04252274	Recruiting	China
Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection	NCT04251871	Recruiting	China
COVIDL1: A Study to Investigate the Efficacy of Tradipitant in Treating Severe or Critical COVID-19 Infection	NCT04326426	Not yet recruiting	
Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	NCT04306393	Recruiting	United States
Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections	NCT03331445	Active, not recruiting	Canada
NK Cells Treatment for Novel Coronavirus Pneumonia	NCT04280224	Recruiting	China
Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	NCT04261907	Not yet recruiting	
A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	NCT04276987	Not yet recruiting	
Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	NCT04308668	Recruiting	United States
STOP PIV - Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects	NCT03808922	Recruiting	United States
Norwegian Coronavirus Disease 2019 Study	NCT04316377	Not yet recruiting	
Lessening Organ Dysfunction With VITamin C	NCT03680274	Recruiting	Canada
Glucocorticoid Therapy for Novel CoronavirusCritically Ill Patients With Severe Acute Respiratory Failure	NCT04244591	Recruiting	China
Convalescent Plasma to Limit Coronavirus Associated Complications	NCT04325672	Not yet recruiting	United States
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	NCT04264533	Recruiting	China
Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure Drug: RoActemra iv, RoActemra sc, Kevzara sc	NCT04322773	Not yet recruiting	Denmark
Safety and Efficacy of Hydroxychloroquine Associated With Azythromycin in SARS-Cov-2 Virus	NCT04322123	Not yet recruiting	Brazil
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	NCT04307693	Recruiting	Korea
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	NCT04292899	Recruiting	United States
NestCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	NCT04315987	Not yet recruiting	
Bevacizumab in Severe or Critically Severe Patients With COVID-19 Pneumonia-RCT (BEST-RCT)	NCT04305106	Recruiting	China
The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia	NCT04273529	Not yet recruiting	
The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19	NCT04273581	Not yet recruiting	
Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	NCT04313322	Recruiting	Jordan
Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA Trial) (HYDRA)	NCT04315896	Not yet recruiting	
Tetrandrine Tablets Used in the Treatment of COVID-19 (TT-NPC)	NCT04308317	Enrolling by invitation	China
Fingolimod in COVID-19	NCT04280588	Recruiting	China
CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment (SAC-COVID)v	NCT04317040	Not yet recruiting	United States
Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19)	NCT04288102	Recruiting	China
The Clinical Study of Carrimycin on Treatment Patients With COVID-19	NCT04286503	Not yet recruiting	
Efficacy and Safety of Corticosteroids in COVID-19(Methylprednisolone)	NCT04273321	Recruiting	China
Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	NCT04318444	Not recruiting	United States
Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial) (PHYDRA)	NCT04318015	Not yet recruiting	
Safety and Immunity of Covid-19 aAPC Vaccine	NCT04299724	Recruiting	China
Immunity and Safety of Covid-19 Synthetic Minigene Vaccine	NCT04276896	Recruiting	China
A Phase I Clinical Trial in 18–60 Adults (APICTH)(vaccine)	NCT04313127	Recruiting	China
Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	NCT04310228	Recruiting	China
Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	NCT04302519	Not yet recruiting	
Multicenter Clinical Study on the Efficacy and Safety of Xiyanping Injection in the Treatment of New Coronavirus Infection Pneumonia (General and Severe)	NCT04295551	Not yet recruiting	
Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)	NCT04303507	Not yet recruiting	
Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19)	NCT04273763	Enrolling by invitation	China
Yinhu Qingwen Decoction for the Treatment of Mild / Common CoVID-19	NCT04278963	Active, not recruiting	China

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Table 1 (*continued*)

Clinical trials	Identifier	Status	country
Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19)	NCT04303299	Not yet recruiting	Thailand
The Effect of T89 on Improving Oxygen Saturation and Clinical Symptoms in Patients With COVID-19	NCT04285190	Not yet recruiting	
Immunoregulatory Therapy for 2019-nCoV: PD-1 blocking antibody + standard treatment, Thymosin + standard treatment, standard treatment	NCT04268537	Not yet recruiting	
Tocilizumab vs. CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS)	NCT04306705	Recruiting	China
Mild/Moderate 2019-nCoV Remdesivir RCT	NCT04252664	Recruiting	China
Losartan for Patients With COVID-19 Requiring Hospitalization	NCT04312009	Not yet recruiting	United States
Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) Drug: Remdesivir, Lopinavir/ritonavir, Interferon Beta-1A, Standard of care	NCT04315948	Not yet recruiting	
Losartan for Patients With COVID-19 Not Requiring Hospitalization	NCT04311177	Not yet recruiting	United States
Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	NCT04273646	Not yet recruiting	China
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	NCT04252118	Recruiting	China
The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia	NCT04261426	Not yet recruiting	
A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia Drug: Abidol hydrochloride, Oseltamivir, Lopinavir/ritonavir	NCT04255017	recruiting	China
A Prospective/Retrospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia Drug: Abidol hydrochloride, Abidol Hydrochloride combined with Interferon atomization	NCT04254874	recruiting	China
Bevacizumab in Severe or Critical Patients With COVID-19 Pneumonia (BEST-CP)	NCT04275414	recruiting	China
A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia	NCT04261270	recruiting	China
Intravenous Aviptadil for COVID-19 Associated Acute Respiratory Distress (COVID-AIV)	NCT04311697	Not yet recruiting	Israel
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia Drug: Methylprednisolone	NCT04263402	recruiting	China
Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19 (NoCovid)	NCT04305457	Recruiting	United States
Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study. (BARI-COVID)	NCT04320277	Recruiting	Italy
Adaptive COVID-19 Treatment Trial (ACTT) Drug: Remdesivir	NCT04280705	Recruiting	United States
Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu Drug: N-acetylcysteine + Fuzheng Huayu Tablet, N-acetylcysteine + Placebo	NCT04279197	Recruiting	China
NO Prevention of COVID-19 for Healthcare Providers Drug: Inhaled nitric oxide gas	NCT04312243	Not yet recruiting	
Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured Patients Drug: Immunoglobulin of cured patients, γ-Globulin	NCT04264858	Not yet recruiting	China
Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients Drug: Recombinant human interferon α1β	NCT04293887	Not yet recruiting	
Experimental Trial of rhIFNα Nasal Drops to Prevent 2019-nCOV in Medical Staff Drug: recombinant human Interferon Alpha-1b, thymosin alpha 1	NCT04320238	Recruiting	China
Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19	NCT04292340	Recruiting	China
Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus	NCT04260594	Not yet recruiting	
Evaluation of Ganovo (Danoprevir) Combined With Ritonavir in the Treatment of Novel Coronavirus Infection Drug: Ganovo + ritonavir+/-Interferon nebulization	NCT04291729	Completed	China
Eculizumab (Soliris) in Covid-19 Infected Patients	NCT04288713	Available	
Severe 2019-nCoV Remdesivir RCT	NCT04257656	Recruiting	China
nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	NCT04306393	Recruiting	United States
Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(CoV) Pneumonia	NCT04269525	Recruiting	China
Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	NCT04261907	Not yet recruiting	
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	NCT04264533	Recruiting	China
Expanded Access Remdesivir (RDV; GS-5734™)	NCT04302766	Available	
Xiyanping Injection for the Treatment of New Coronavirus Infected Pneumonia	NCT04275388	Not yet recruiting	
Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Prevent SARS-CoV-2 Infection	NCT04283461	recruiting	United States
Tocilizumab for SARS-CoV2 Severe Pneumonitis	NCT04315480	Not yet recruiting	Italy
Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	NCT04252274	recruiting	China
Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	NCT04261517	Completed	China
Treatment and Prevention of Traditional Chinese Medicines (TCMs) on 2019-nCoV Infection Drug: Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir) and Traditional Chinese Medicines (TCMs) granules, Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir)	NCT04251871	recruiting	China
Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia	NCT04275245	recruiting	China
Stem Cell Educator Therapy Treat the Viral Inflammation Caused by Severe Acute Respiratory Syndrome Coronavirus 2	NCT04299152	Not yet recruiting	
NK Cells Treatment for Novel Coronavirus Pneumonia	NCT04280224	Recruiting	China
Glucocorticoid Therapy for Novel CoronavirusCritically Ill Patients With Severe Acute Respiratory Failure Drug: methylprednisolone therapy	NCT04244591	Recruiting	China
Norwegian Coronavirus Disease 2019 Study Drug: Hydroxychloroquine Sulfate	NCT04316377	Not yet recruiting	
Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	NCT04276688	Recruiting	China
Post-exposure Prophylaxis for SARS-Coronavirus-2 Drug: Hydroxychloroquine	NCT04308668	Recruiting	United States
A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	NCT04276987	Not yet recruiting	
Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID19 Infection	NCT04290858	Withdrawn	
Nitric Oxide Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19.	NCT04290871	Withdrawn	

months to test their efficacy *in vitro* and *in vivo*, and the results of clinical trials may take even longer. In order to shorten this time, WHO is organizing a large clinical trial (Solidarity clinical trial), encompassing over 100 countries from all around the world.

8.1. Virally targeted agents

Antiviral drugs and systemic corticosteroids, including neuraminidase inhibitors (Oseltamivir, Peramivir, and Zanamivir), Ganciclovir, Acyclovir, and Ribavirin, as well as Methylprednisolone which reduced the risk of death in ARDS patients [63–65], are used in the clinic for viral infections. However, they have not been shown to have any effect on COVID-19, thus they are not recommended [66].

8.1.1. Nucleoside analogs

Nucleoside analogs are derivatives of adenine or guanine that block the RNA-dependent RNA polymerase enzyme and affect the structure of viral RNA in a large spectrum of RNA viruses, including human coronaviruses [67].

8.1.1.1. Favipiravir (T-705). Favipiravir is a guanine analog that is approved for influenza treatment. It can inhibit the RNA-dependent RNA polymerase of RNA viruses such as Influenza, Yellow fever, Chikungunya, Ebola [68], Norovirus, and Enterovirus [67]. Besides, in one recent study, scientists have reported its effectiveness against 2019-nCoV [69]. Patients with COVID-19 are being enrolled in randomized clinical trials to test the efficacy of Favipiravir plus Interferon-α (ChiCTR2000029600), and Favipiravir plus Baloxavir marboxil (an approved Influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544).

8.1.1.2. Favilavir. Favilavir is an approved treatment for Influenza, which inhibits the RNA-dependent RNA polymerase. It has been approved as an experimental coronavirus drug against SARS-CoV-2 [70].

8.1.1.3. Ribavirin. Ribavirin is a guanine derivative approved for treating respiratory syncytial virus (RSV) and hepatitis C virus (HCV) infections, which also showed positive results in patients with SARS and MERS, but its side effects such as anemia may be severe at high doses [71]. Besides, its potency against SARS-CoV-2 is unknown [72,73]. One in-silico study revealed the potential ability of Sofosbuvir, Ribavirin, and Remdesevir to inhibit SARS-CoV-2 polymerase [74]. However, another study, mentioned above, ruled it out as an effective therapy for COVID-19. So, it is not yet clear whether it is effective against COVID-19 or not, and more investigation is needed.

8.1.1.4. Remdesivir (GS-5734). Remdesivir is a phosphoramidite prodrug of an adenine derivative with a chemical structure similar to Tenofovir alafenamide, an approved inhibitor of HIV reverse transcriptase. Remdesivir had broad-spectrum activity against a diverse range of coronaviruses, including human CoVs, zoonotic bat CoVs, and pre-pandemic zoonotic CoVs, in addition to Ebola in cell culture and animal models [75]. The results of the latest studies suggested that Remdesivir can inhibit 2019-nCoV [69,76]. Moreover, a phase III clinical trial of Remdesivir against COVID-19 was launched in Wuhan on February 4th, 2020. Remdesivir is not expected to be widely available as an experimental drug for treating a vast number of patients [77]. However, the Food and Drug Administration (FDA) has approved Remdesivir as an effective COVID-19 treatment [78].

8.1.1.5. Galidesivir (BCX4430). Galidesivir is an adenosine analog that was initially developed to treat HCV, and its efficacy against Yellow fever revealed its antiviral activity in preclinical studies against many RNA viruses, including SARS-CoV and MERS-CoV [71]. At present, it is in primary clinical trials to assess its safety in healthy individuals. So, it

might be useful against SARS-CoV-2.

8.1.1.6. Protease inhibitors

8.1.1.6.1. Chymotrypsin-like (3C-like protease, 3CLpro) and papain-like protease (PLP) inhibitors. 3C-like protease or 3CLpro and PLP are non-structural proteins, which play a critical role in the replication of coronaviruses, and can also inhibit the host innate immune responses [79]. So, 3CLpro inhibitors and PLP inhibitors might be effective against SARS-CoV-2.

8.1.1.6.2. Lopinavir. Lopinavir was primarily supposed to inhibit the 3-chymotrypsin-like protease of SARS and MERS. Although it improved the clinical outcomes in SARS patients in a non-randomized open-label trial [71], it is questionable whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2 or not. This is because the molecular design of HIV protease inhibitors was explicitly optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer, however, this C2-symmetric pocket is absent in coronavirus proteases [80]. In contrast to previous studies that showed after administration of Lopinavir/Ritonavir, β-coronavirus the viral loads were significantly reduced, and coronavirus titers were low or absent [81], it has been shown that the combination of Lopinavir and Ritonavir is not effective in treating patients with severe COVID-19 [82].

8.1.1.6.3. Disulfiram. Disulfiram is a drug used for treating chronic alcoholism by inducing an acute intolerance to ethanol (drinking alcohol). Disulfiram was reported to inhibit the papain-like protease of MERS and SARS in cell culture, but clinical evidence is lacking [83]. It could be effective against SARS-CoV-2, but further investigations are needed.

8.1.1.6.4. Other 3CLpro inhibitors and PLP inhibitors. Other 3CLpro inhibitors, such as Cinanserin [84], Flavonoids [85], Cobicistat [86], Atazanavir, Efavirenz, Ritonavir, Dolutegravir [87], Thymopentin, Carfilzomib, Saquinavir [88], Ledipasvir, and Velpatasvir [89] and PLP inhibitors, like Diarylheptanoids [90], Grazoprevir, Telaprevir, Boceprevir [91], Darunavir [92], and Formoterol chloroquine [93] are other potential approaches to combat SARS-CoV-2, but their efficacy remains to be tested.

8.1.1.6.5. Danoprevir. Danoprevir is an NS3/4A protease inhibitor that is used as an anti-HCV drug. It interferes with virus replication and suppresses the effects of the virus on the host response to viral infection. In a small clinical trial of 11 COVID-19 patients, after 4 to 12 days of use of Danoprevir, all the patients recovered [94]. So, it might be suggested that Danoprevir could be effective against SARS-CoV-2.

8.1.1.6.6. Camostat mesylate. Scientists reported in one study how the spike-like glycoprotein of the SARS-CoV-2 virus binds to the ACE2 receptor. Accordingly, the presence of transmembrane protease serine2 (TMPRSS 2) is required for spike protein priming. The researchers found that Camostat mesylate, a serine protease inhibitor, could block the entry of SARS-CoV-2 into lung cells. So, it might be effective against COVID-19. However the application of this drug as a treatment for COVID-19 requires clinical trials [95].

8.1.1.6.7. Griffithsin. Griffithsin has antiviral effects against HCV and HIV *in vitro* [96,97]. It is a red-alga-derived lectin, which binds to oligosaccharides on the surface of various viral glycoproteins, including HIV glycoprotein 120 and SARS-CoV spike glycoprotein [71]. Besides, it can inhibit virus entry, reverse transcriptase activity, integrase activity, and protease activity [98]. So, it might be effective against SARS-CoV-2, but further investigation is needed.

8.1.1.7. Arbidol. Arbidol is a non-nucleoside antiviral and immunomodulatory drug for treatment and prevention of influenza, which could be effective against COVID-19 [99]. Several clinical trials for investigating its effectiveness against COVID-19 are in progress.

8.2. Chloroquine (CQ) and Hydroxychloroquine (HCQ)

CQ is an anti-malarial drug [100] with practical activity against SARS-CoV-2 infection [101], which could help in the treatment of COVID-19. It has immunomodulatory effects, such as suppression of the production and release of tumor necrosis factor-α (TNF-α), and Interleukin (IL-6). It also works as a novel type of autophagy inhibitor [102], which probably interferes with viral infection and replication. Moreover, scientists have reported in a number of studies that CQ interferes with the glycosylation of the cellular ACE2 receptor, the spike protein of SARS-CoV, and the entry of the virus [101,103]. Besides, CQ increases the pH of acidic intracellular organelles such as endosomes and lysosomes, which are essential for membrane fusion [104]. So, this drug can reduce fever and improve the radiological characteristics of the lungs in COVID-19. Also, it reduced the time to recovery. Besides, CQ is one of three drugs that could be promising for the treatment of new coronavirus disease; the other two drugs, described above, are Favipiravir and Remdesivir [105], where the percentage of patients with a negative viral nucleic acid test was higher with anti-malarial drugs. Until now, no severe side effects have been reported in more than 100 participants treated with CQ in trials. It has been shown that oral absorption of CQ and HCQ in humans is useful in SARS-CoV-2 treatment. Because HCQ was less toxic than CQ in animal models [106], and considering that an overdose of CQ could result in acute poisoning and death [107]; the safe dosage (6–6.5 mg/kg per day) [108] of HCQ sulfate could effectively treat SARS-CoV-2 infections. It must be mentioned that although the combination of HCQ plus Azithromycin c was an effective treatment of COVID-19 [109], the NIH has not recommended it as a routine treatment for clinical use due to the potential for toxicity.

8.3. Cytokine-based therapy

The cytokine storm or cytokine release syndrome (CRS) results from the widespread release of pro-inflammatory cytokines following the activation of the immune system by microorganisms or even by therapeutic interventions [110]. In SARS-CoV and MERS-CoV infections, overproduction of pro-inflammatory cytokines, such as IL-6, IL-1β, IL-12, IL-18, IL-33, Interferon-α (IFN-α), IFN-γ, and TNF-α, or chemokines such as chemokine C-C motif ligand2 (CCL-2), CCL-3, CCL-5, C-X-C motif chemokine ligand 8 (CXCL-8), CXCL-9, and CXCL-10 were included in the cytokine storm [111–113]. It has been shown that by activating type 1 macrophages (M1) and T-helper 1 (Th1) cells, COVID-19 increases the production of inflammatory cytokines like IL-6, IFN-γ, and granulocyte monocyte-colony stimulating factor (GM-CSF) [114]. It must be mentioned that IL-6 and GM-CSF (can significantly enhance the production of IL-6 by stimulating monocytes [115,116]) which are secreted by monocytes and T cells, are more important in inducing the cytokine storm than other pro-inflammatory cytokines.

The cytokine storm is one of the fundamental causes of COVID-19 pathogenesis, resulting in excessive inflammation, lung damage, ARDS, and other organ failure. Also, the presence of high levels of TNF-α, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein 1A (MIP-1A), monocyte chemoattractant protein-1 (MCP-1), CXCL-10, IL-10, and IL-7 in severe COVID-19 patients indicates the importance of CRS in the disease progression [16]. So, CRS is considered to be a principal cause of death in COVID-19 patients [117,118].

Therefore, it is important to investigate the control of CRS through various methods like immunomodulation approaches, mesenchymal stem cells (MSCs), or Interferon-based therapy [119].

8.3.1. Immunomodulation approaches

8.3.1.1. Monoclonal antibodies (mAb).
As mentioned before, IL-6 is an important component of the cytokine storm. So, the use of anti-IL-6 inhibitory agents, like Tocilizumab, Sarilumab, Siltuximab, which are all humanized mAbs, might reduce the adverse effects of CRS [17]. It must be noted that anti-GM-CSF mAbs like TJ003234, Gimsilumab, and Lenzilumab are also being evaluated against COVID-19. Moreover, inhibitors of the IL-1 family, IFN-γ cytokines, and the Janus kinase signal transducer and activator of transcription proteins (JAK-STAT) signaling pathway might also be useful for controlling the cytokine storm [120].

8.3.1.2. Hyaluronidase and 4-Methylumbelliferone (4-MU).
It has been demonstrated that the increased levels of pro-inflammatory cytokines, including IL-6, IL-1, and TNF-α in the lungs of COVID-19 patients, can result in the production of hyaluronan or hyaluronic acid (HA) by inducing the expression of HA-synthase-2 (HAS2) this may contribute to ARDS and death [117,121]. So, lowering HA levels through administration of hyaluronidase, or 4-methylumbelliferone (4-MU), and blocking the inflammatory cytokines could be effective for treating dyspnea and reducing the mortality rate of COVID-19 patients [122].

8.3.1.3. Corticosteroids.
Corticosteroids can be useful in controlling CRS, for instance in cancer immunotherapy. Initially, dexamethasone was proposed as an effective agent for managing CRS. However, due to the enhanced risk of vascular necrosis and diabetes (which are mortality risk factors for COVID-19), corticosteroid administration for COVID-19 patients is not recommended [123].

8.3.1.4. Immune cell depletion.
Immune cells are responsible for the secretion of inflammatory factors. So, decreasing the lymphocyte count might result in CRS suppression. Rituximab, Etoposide, and Lenumab are Mabs used to reduce CD8$^+$ T cells, decrease the release of interferon-gamma, and to treat CRS and hemophagocytic lymphohistiocytosis (FHLH) [124,125].

8.3.1.5. Interferon-based therapy.
Interferons regulate the innate immune system, which is vital for killing viruses by regulating gene transcription [126]. IFNs regulate the transcription of genes through activating the JAK-STAT signaling pathway after binding to their receptors on the cell surface. IFN type1 is composed of IFN-β and IFN-α, and IFN-α2b has been shown to rapidly suppress the replication of animal and human coronaviruses [127]. SARS-CoV-2 can inhibit the activity of IFN type1 through the suppression of the STAT-1 intracellular signaling pathway [128]. So, IFN-based therapies could be useful for treating COVID-19.

Interestingly, the low morbidity and mortality rates of COVID-19 in children might be due to the low secretion threshold of IFNs in children, and the rapid production of IFNs after infection. Thus, the high secretion threshold of IFNs in adults could be responsible for the higher mortality rate in these patients. So, IFN-based therapies might be effective against COVID-19, especially in the early phase of the disease [128].

In addition to the direct suppression of the SARS-CoV-2, which could contribute to the therapeutic response, IFN-based therapy can stimulate the innate immune. So, pegylated IFNα-2a and IFNα-2b could be tested in patients with COVID-19, as they stimulate innate antiviral responses.

Nevertheless, clinicians must be wary of administering IFNs alone, due to the possibility of increasing the cytokine storm with high doses of IFNs.

8.3.1.6. Stem-cell therapy.
Stem-cell therapy has demonstrated a possible therapeutic benefit in almost all incurable diseases [128]. Among stem cells, MSCs have received most attention because of their many advantages. These include, a high proliferation rate, self-renewal ability, reparative properties, availability from different tissues, multidirectional differentiation, lack of adverse reactions, and long-term storage ability. In addition to tissue regeneration, they are used for

their anti-inflammatory and immunoregulatory activity [129]. Chinese scientists have reported the use of MSCs as an anti-inflammatory approach to cytokine storm-like disorders. So, they could be effective in controlling CRS.

MSCs based immunomodulatory activities include suppressing the over-activation of T cells and macrophages

stimulating the anti-inflammatory macrophage 2 phenotype (M2)

stimulating T-regs

and suppressing pro-inflammatory cytokines. MSC-based therapy might decrease the risk of CRS in COVID-19 patients by reducing the production of TNF-α, IFN-α, IL-1, IL-6, and IL-12 [130].

Moreover, MSCs might improve ARDS, regenerate lung tissue, and lessen lung fibrosis through secreting IL-10, vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) in SARS-CoV-2 patients [130]. It is possible that MSC-based therapy could remove the need for ventilation in COVID-19 patients, return the T cell counts to a normal range, restore pulmonary function, decrease the level of inflammatory cytokines, and increase the level of anti-inflammatory cytokines [131,132].

In order to improve the effectiveness of MSC-induced anti-inflammatory response, they could be pretreated using IFN-γ, which is low or absent in severe COVID-19 [133].

These cytokine-licensed MSCs could be more effective in the suppression of hyperactive immune response and promotion of tissue repair, because it is known that cytokine-licensed MSCs were effective in preventing lipopolysaccharide (LPS)-induced acute lung damage [134]. So, several clinical trials are being carried out for evaluating the effectiveness of MSCs against COVID-19.

8.4. Passive antibody therapy and convalescent plasma therapy

Plasma antibodies contribute to the elimination of infection via directly binding to pathogens and neutralizing them, or by activating indirect immune responses, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, or phagocytosis [135,136]. In COVID-19 patients, their plasma contains active specific neutralizing antibodies (which mediate the anti-infective function of plasma therapy) and non-neutralizing antibodies (which might boost prophylaxis and improvement of patients).

Hyper-immune immunoglobulin therapy or convalescent plasma (CP) is a passive-adaptive-immunotherapy applied to protect individuals from clinical infection or prevent disease development. The early administration of CP or hyper-immune immunoglobulin that contains high antibody titers could decrease the viral load, reduce disease mortality, and shorten hospital stays [137,138].

While passive antibody therapy involves the pooling of immunoglobulin preparations with high antibody titers, plasma therapy is applied as an emergency treatment, especially in epidemics and pandemics, when there is limited time or resources for pooled immunoglobulin preparation. Compared to passive antibody therapy which generates short-term rapid immunity, persistant immunity is produced by monoclonal antibodies or hyper-immune globulin (fractionated plasma products) [139]. Therefore, convalescent plasma is employed as a rapid immune-based therapy in the early stages of the disease [140], to increase infected patients immunity against the virus, stop COVID-19 progression, and enhance the therapeutic success rate [141]. Moreover, plasma therapy can decrease viremia and reduce new infections (through neutralizing antibodies), clear free virus and infected cells, and alleviate the symptoms (like dry cough, fever, sputum, muscle pain) and pulmonary damage. Moreover, it can increase the lymphocyte ratio and blood oxygen saturation without any adverse effects [141–144].

The FDA has approved the administration of convalescent plasma containing specific antibodies against SARS-CoV-2 [145]. Besides, the FDA has recommended that people who have recovered from COVID-19 (for at least two weeks) should donate their plasma to help other patients. It is estimated that each donation can provide sufficient plasma for four patients [146].

However, there are some challenges in the collection of plasma from donor serum during the recovery period or after recovery, and confirming the proper level of neutralizing antibody titer. Some of these challenges are the availability of willing qualified donors, clinical conditions, eliminating host interactions, and the viral kinetics of SARS-CoV-2, that will need to be solved before convalescent plasma can become a generalized therapeutic option.

A qualified donor must be selected based on a confirmed history of COVID-19 infection, including a negative follow-up molecular test, the absence of symptoms, normal physical examination, and pre-donation screening assays. It should be mentioned that since plasma with a high neutralizing antibody titer is only obtained at 14 days after the resolution of symptoms, this is the best time to harvest the plasma [143]. Besides, it has been suggested that apheresis might be better for optimizing the convalescent plasma product, rather than whole blood donation. The appropriate dose convalescent plasma therapy in COVID-19 was determined based on past experience of applying plasma therapy in SARS-CoV, which was 5 mL/kg of plasma with ≥ 1:160 titer [140].

It must be taken into account that transfusion-transmitted SARS-CoV-2, acute transfusion-related injuries, other transfusion-transmissible infections, transfusion-associated circulatory overload, and allergic transfusion reactions could be risks of plasma therapy in the treatment of COVID-19 [147,148].

It must be mentioned that in some patients, COVID-19 antibodies are not always found after recovery, which suggests that some patients recover without antibodies [149] or else the antibodies vanish after recovery. Although one study evaluated the effectiveness of plasma therapy in five patients (who were mechanically ventilated and received methylprednisolone) all of them showed a reduction in COVID-19 symptoms and viral load, it is not yet clear that the antibodies from donors are active and effective or not [150].

Even considering the risks of plasma therapy, it could still be effective as an emergency COVID-19 treatment.

8.5. Monoclonal antibodies (mAbs)

Monoclonal antibodies (mAbs) can be obtained from COVID-19 patients or by laboratory preparation. They are characterized by high specificity and purity, high safety, and a low rate of blood-borne infections that can overcome the limitations of intravenous immunoglobulins and convalescent plasma therapy. mAbs can be chosen to target the specific epitopes of surface SARS-CoV-2 proteins and could inhibit the virus entry into host cells (including receptor binding, membrane fusion, and sialic acid-binding sites), and reduce replication and infection progression.

Some mAbs that target the spike protein in SARS-CoV and MERS-CoV have shown promising results *in vitro* and *in vivo*, that could be potentially useful against SARS-CoV-2 [151]. For example, specific neutralizing mAbs against the receptor-binding domain (RBD) in spike protein (CR3014 [152], CR3022 [153], 311mab–31B5, 311mab–32D4, and 311mab–31B9), or specific mAbs that bind to ACE2 could all effectively block virus entry [139]. It must be mentioned that contrary to 311mab–31B9 (without any neutralization capability) [154], 311mab-31B5 and 311mab-32D4 can both potently suppress the SARS-CoV-2 RBD protein and interaction with the human ACE2 (hACE2) protein, leading to virus neutralization. Moreover, using CR3022 as a monotherapy, or else in combination with other drugs might result in COVID-19 patient improvement. Besides, 47D11 could powerfully suppress the infection of SARS-CoV and SARS-CoV-2 through an unknown mechanism [155].

Furthermore, m396, CR3014 [156], and Meplazumab (which is an anti-CD147 Mab [157], could be alternative monoclonal antibodies to be used against SARS-CoV-2 [153]. So, mAbs can be considered as potential therapeutic options against COVID-19.

8.6. Polyclonal antibodies

Polyclonal antibodies can be used as prophylactic or therapeutic agents against viral infections [75]. For example, SAB-301 is a well-tolerated antiviral treatment for MERS-CoV [158]. So, polyclonal antibodies might also be effective against COVID-19.

8.7. Intravenous immunoglobulin (IVIg)

IVIg is an effective immunomodulatory agent, which has been applied in autoimmune and inflammatory diseases, bacterial infections, severe viral infections, fungal infections, and also in graft versus host disease (GVHD). It is composed of polyclonal immunoglobulin G or IgG. IVIg can modulate the immune system through various mechanisms, like reducing and preventing the production of cytokines, enhancing anti-inflammatory cytokines, and inducing immune system responses against the virus [159]. IVIg has been used to treat infections of the upper and lower respiratory tracts [160,161]. Besides, IVIg therapy showed a clinical benefit and good tolerability in SARS and MERS cases [162,163]. So, IVIg therapy could be a potential therapeutic option against COVID-19 [59]. High-dose IVIg therapy, 0.3–0.5 g per kg body weight over five days, has been proposed for COVID-19 patients. Scientists have shown that the application of high-dose IVIg at the appropriate time point could prevent disease progression to a severe state and enhance the patient recovery rate in early phases of the disease. Moreover, after administration of IVIg no adverse effects were reported [164]. So, immunotherapy with IVIg either alone or in combination with other anti-SARS-CoV-2 therapies could be an alternative option for COVID-19 patients.

8.8. Anakinra

In one small retrospective cohort study in Italy, the effect of Anakinra, a recombinant Interleukin-1 receptor antagonist, was studied in the treatment of COVID-19. In this study, 29 patients received the drug, while 16 patients received only standard treatment for COVID-19. Twenty-one patients (72%) of the intervention group had a CRP level below the standard after 21 days, and most of them recovered; while five patients were mechanically ventilated, and three died. Only eight (50%) of the 16 control patients had improved respiratory status after 21 days, of which one person was mechanically ventilated, and seven died. Survival rates at 21 days in the intervention and control groups were 90% and 56%, respectively with a significant difference. Anakinra could increase the survival of patients with COVID-19 and improve respiratory status, and may be an effective treatment [165].

8.9. Ibuprofen

Ibuprofen has shown problems with safety [166]. Discussions over the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of COVID-19 has involved the European Medicines Agency. It had been proposed that NSAIDs could be considered for treating the emerging viral illness in some cases, but most patients with COVID-19 symptoms should use Paracetamol rather than Ibuprofen, because the latter could worsen the condition. Reports in French media showed a deterioration in the condition of four young people with COVID-19 after taking Ibuprofen [167]. So, it is wise to use Paracetamol instead of Ibuprofen for COVID-19 patients.

8.10. Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blocker (ARB)

It had been suggested that the use of ACE-I and ARB drugs for cardiovascular indications could lead to an up-regulation of ACE2 receptors, and hence the development of more severe COVID-19 [168]. However, the European Heart Association as well as three major American cardiology bodies, including the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America, have all emphasized that patients who have been taking ACE-I or ARB drugs should continue their treatment.

8.11. Human recombinant solution ACE2 (hrsACE2)

The hrsACE2 solution, previously clinically tested in phase one and two clinical trials (2017), could significantly inhibit COVID-19 infection in the early stage and prevent the virus from attaching to the cell. It reduced SARS-CoV-2 levels in Vero-E6 cells (cells used for virus isolation) up to 1000–5000 times (in terms of viral load) in laboratory studies [169]. It must be mentioned that this study had some limitations, for example, lung organoids were not tested, and the experiment only simulated the early stages of COVID-19. So, because SARS-CoV-2 can directly infect human blood vessels and enter the kidneys, and hrsACE2 could prevent this occurrence, it might be used in the clinic. However, further investigations are needed.

8.12. CRISPR Cas13

Clustered regularly interspaced short palindromic repeats (CRISPR) is a novel genome engineering tool, which is composed of two components, including a guide RNA (gRNA), which is specific to the target DNA or RNA sequence, and a non-specific CRISPR associated endonuclease protein or Cas protein.

CRISPR Cas13 is a type VI CRISPR-associated RNA-guided ribonuclease, which targets a specific sequence of RNA. Three protein families have been recognized, including Cas13a (formerly known as C2c2), Cas13b, and Cas13c [170,171]. Cas13a enzymes can also be a suitable tool for nucleic acid sequence detection [172]. In addition, since Cas13 and inactive Cas13 target specific RNA sites for cleavage and inhibition, respectively, they could be used as an effective COVID-19 therapy. However, further investigations are essential.

8.13. Nitric oxide

Newborns with severe ARDS, are treated with high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation. This approach might be effective for patients of COVID-19 with ARDS [173,174] as well.

8.14. Oxygen therapy

Almost all patients are administered oxygen therapy, and WHO has recommended extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia [175].

8.15. Lithium

Because lithium reduces apoptosis and inhibits glycogen synthase kinase3 beta (GSK-3β), which interacts with receptors and triggers signal transduction events, it might be effective against COVID-19 [176].

8.16. Antibiotics

Antibioticshave been suggested for alleviating the pneumonitis symptoms, and it was shown in an *in vitro* study that Teicoplanin could prevent the entry of SARS-CoV-2 into the cytoplasm [177]. Moreover, Azithromycin has shown some success against COVID-19.

8.17. Ivermectin

Ivermectin is an FDA-approved drug for the treatment of parasitic amnesia, which is widely available. It was shown in one study that

adding five μM of Ivermectin to virus-infected Vero/hSLAM cells reduced the levels of viral RNA by 5,000 times after 48-hour culture [178]. So, it could be effective against COVID-19.

8.18. Nitazoxanide

Nitazoxanide is an antidiarrheal drug that has been proposed to inhibit 2019-nCoV [69], but more investigation is needed. Besides, the combination of Nitazoxanide and Azithromycin could be more effective than using them as single agents against COVID-19 [179]. Nevertheless, combining several therapies may increase the side effects and lead to drug-drug interactions, which must be taken into account when proposing new treatments for COVID-19.

8.19. Bacillus Calmette–Guérin (BCG)

Bacillus Calmette–Guérin (BCG) vaccination is being considered in clinical trials to test its efficacy to decrease COVID-19 morbidity and mortality rates [179].

8.20. Colchicine

Colchicine has an immunomodulatory effect, and is commonly used in the treatment of gout. Due to its immunomodulatory effects, it could be useful for ameliorating the clinical manifestations of COVID-19 [180].

Because of the wide variety of therapeutic options either as a single drug or in combination with other drugs, it is difficult for clinical trials to be conclusive. This is why WHO is conducting the Solidarity clinical trial; up to April 21st, 2020, over 100 countries have joined this clinical trial to defeat SARS-CoV-2. [181].

8.21. Vitamins

It has been demonstrated in several studies that vitamin B3 (niacin or nicotinamide) was effective in reducing injury in animal models with bleomycin-induced lung damage [182]. Vitamin C could also be effective in preventing COVID-19 as it can reduce the severity of lower respiratory tract infections [183]. Moreover, It was suggested that the supplementation with vitamin D and vitamin E might increase resistance to SARS-CoV-2 [184]. Thus, vitamin supplements might be worth combining with other therapies in patients with COVID-19.

9. Clinical trials

At the time of the preparation of this study (March 29th, 2020), more than 200 clinical trials of COVID-19 had been listed in https://clinicaltrials.gov/. Trials involving vaccines, antiviral drugs, immunotherapies, monoclonal antibodies, stem cells, and nitric oxide are summarized in Table 1.

10. Conclusion

In conclusion, SARS-CoV-2 is a novel and highly contagious virus, and there is no specific treatment for COVID-19 disease up to now. It must be taken into account that if no effective action is taken and if drugs, vaccines, and patient tracking measures are not widely implemented or effective, intermittent social distancing is likely to continue until 2022. By that time COVID-19 might have affected 90% of the world population and kill over 40 million people [185,186]. Therefore, it is wise to continue preventive methods and public health measures until an appropriate vaccine and effective drugs are discovered. Combinational therapies with some of the above-mentioned drugs or supplements, plus an appropriate immunomodulatory diet, proper mental support and adherence to standards, will eventually be effective against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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